Efficient Electrosynthesis of Thiazolidin-2-imines via Oxysulfurization of Thiourea-Tethered Terminal Alkenes using the Flow Microreactor

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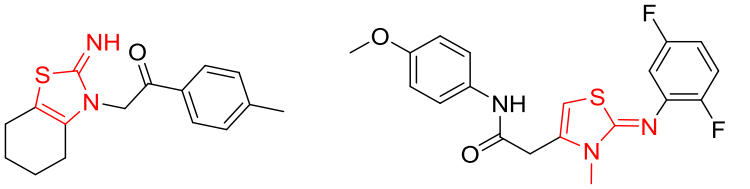
Abstract: *Sulfur-containing scaffolds play a significant role in many important biological processes. The thiazole-2-imine derivatives have gained significant biological attention due to their interesting pharmacological activities and act as potential therapeutic agents. Many of their syntheses suffer from the drawbacks such as the handling of toxic reagents, harsh reaction conditions, longer reaction times and tedious separation procedures. To their easy access, we applied first time flow electrochemical approach under free supporting electrolytes conditions and without the use of expensive catalysts and reagents. This is not only the first electrochemical cyclisation to access thiazolidin-2-imines also represents the first intramolecular sulfurisation of unfuctionalised terminal alkenes. This flow electrolysis of N-allylic thioureas generates radical intermediates of nitrogen and sulfur that cyclised via oxysulfurisation of terminal alkenes and gives thiazolidin-2-imines with good to high yields under mild, green and environmentally friendly conditions.*

Chemistry is the development of new synthetic methods using microreactor technology that provide more efficient and environmentally sustainable alternatives to established methodologies.[1] Herein, we describe the flow electrolysis of *N*-allylic thioureas for the oxysulfurization of terminal alkenes to easily access biologically important scaffolds such as thiazolidin-2-imines.[2] The thiazole-2-imine derivatives have gained significant biological attention due to their interesting pharmacological activities such as anti inflammatory, analgesic, kinase inhibition activities[3] anti bacterial,[4] anti fungal,[5] melanin reducing activity,[6] anti convulsant[7] anti viral,[8] and anti parasitic.[9] Pifithrin has a 2-imino-thiazoline moiety (Figure 1)



Pifithrin: p53 inactivator **KHG22394:** skin whitening agent

Figure 1. Structures of pharmacological important molecules with a thiazole-2-imine core.

and is a key chemical inhibitor of p53.[2] It acts as a potential therapeutic agent due to its applications for the cure of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, cancer therapy, stroke, and other signalling related pathologies.[10]

In 1887, the Hantzsch thiazole synthesis using the condensation of α-haloketones with thiourea was established.[11] A few routes for the synthesis of thiazolidin-2-imines have been reported in the literature.[12–15] Amongst them, a few important methodologies which have been recently developed are illustrated in Figure 2. Dethe and co-workers have reported a synthesis of thiazolidine-2-imines by a multicomponent reaction of imines, terminal alkynes and isothiocyanates in the presence of a chiral copper-pybox complex as catalyst (Figure 2a).[13] Sun and co-workers have developed a one-pot synthesis of 2-imino-1,3-thiazolidines and 2- imino-1,3-thiazolines on a soluble support using ionic liquid tethered 2-aminobenzimidazoles, isothiocyanates and 1,2-dichloroethane (Figure 2b).[14] Very recently, Li and co-workers have developed a synthetic route to thiazole-2-imines involving phenacyl bromide, amine and phenyl isothiocynate with trypsin as a biocatalyst (Figure 2c).[15] However, all these methods suffer from a few drawbacks such as the handling of toxic isocyanides and bromine sources, harsh reaction conditions, longer reaction times and tedious separation procedures. Wang and co-workers[16] described the first reaction

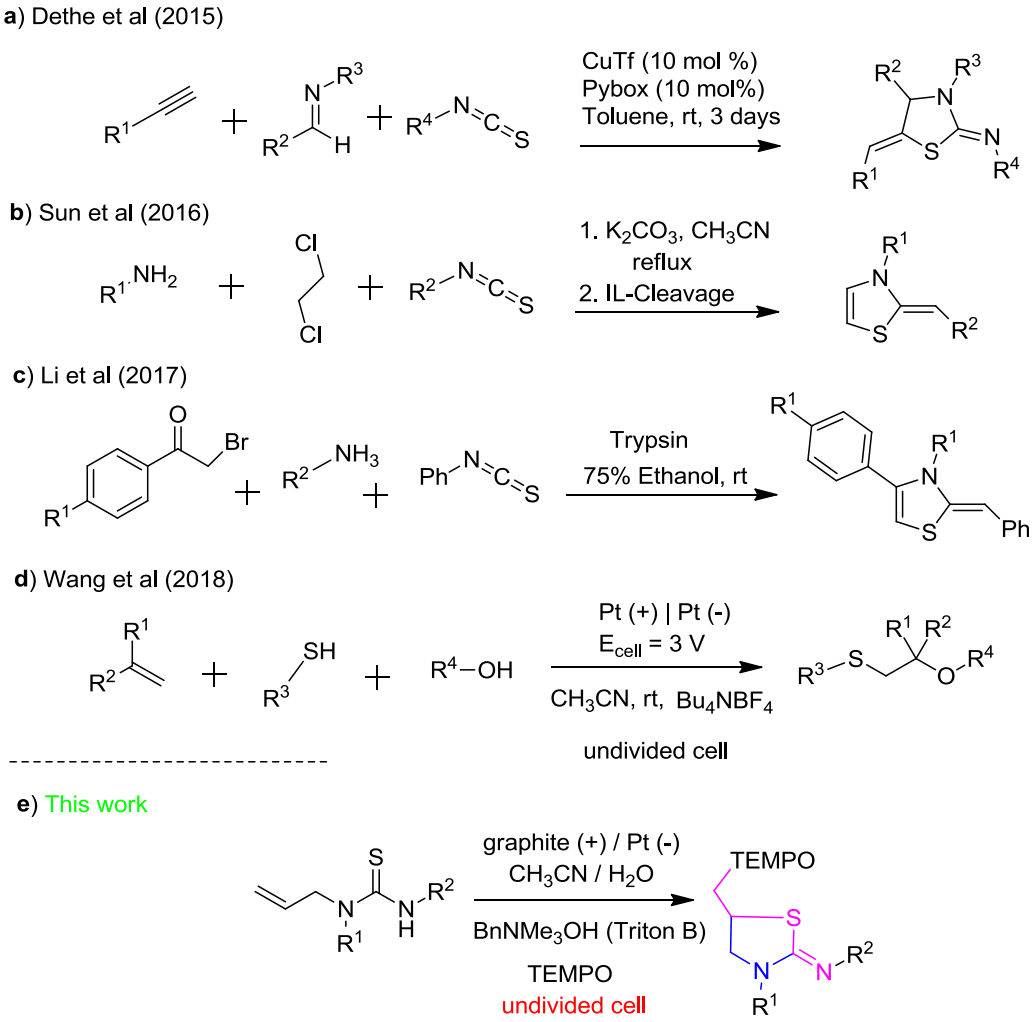
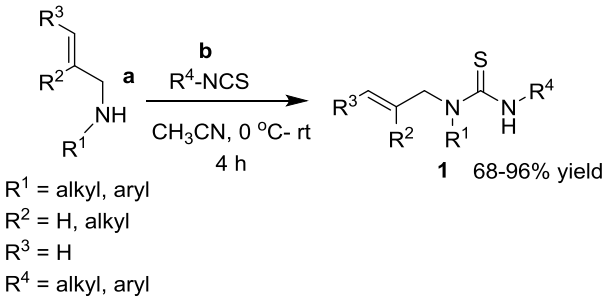


Figure 2. Current state of the related works.

of intermolecular electrochemical oxidative oxysulfurization of olefins with thiols and nucleophilic oxygen sources through two cascade oxidations at the anode under catalyst and oxidant free conditions, at room temperature (Figure 2d). This reaction showed wide substrate scope, broad functional group tolerance and excellent regioselectivity, being a new and green strategy for the difunctionalization of olefins. However, several electrolytes (such as NaCl, Bu_4NBr and Bu_4NBF_4) were used to optimize reaction conditions.

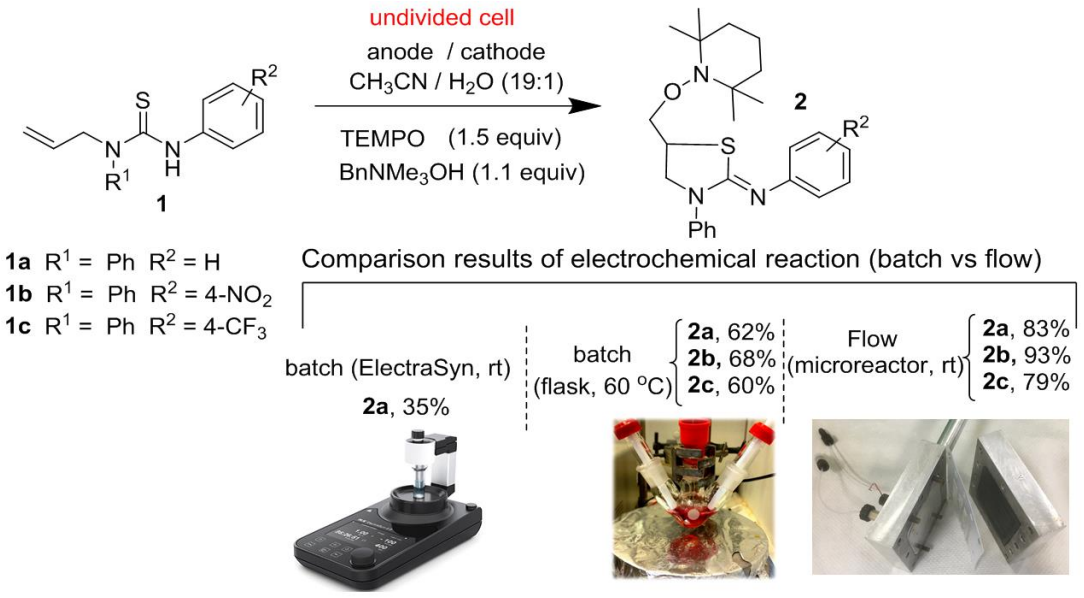
The use of electrical energy to induce chemical transformations constitutes an interesting and green activation mode of organic molecules. It offers an alternative route for organic synthesis using the electric current as a reagent. This is an extremely clean route for the formation of radical intermediates and allows the reversal of functional group polarity through single-electron transfer processes. Electrochemistry typically avoids expensive catalysts and ligands and enables green chemical transformations.[17] The batch electrolytic reactions suffer from disadvantages such as inhomogenicity of the electrical field and the obligatory use of electrolytes. Flow electro-microreactor technology can effectively overcome these difficulties. New reactions can benefit from the physical properties of microreactors, such as enhanced mass- and heat transfer due to a very large surface to volume ratio as well as regular flow profiles leading to improved yields.[1] We used the chip-type electro-microreactor for the synthesis of thiazolidin-2-imines that was easy to handle during flow reactions (see detail in supporting information). With this arrangement, different electrodes, electrode combinations with multiple layers, ion-exchange membrane, spacers and ultrasound can be used for efficient electrochemical transformations.[1d]

For the synthesis of thiazolidin-2-imines via oxysulfurisation of terminal alkenes, we synthesised number of *N*-allylic thioureas (Scheme 1, see supporting information for detail). Initially, we used *N*-allylic thiourea **1a** as a standard substrate for the electrochemical synthesis of thiazolidin-2-imine **2a**. Initial batch electrosynthesis was tested in ElectraSyn-based undivided cell at room temperature using a graphite anode and a platinium cathode as electrodes with constant current of 10 mA and up to 10 F of electricity was passed through the reaction mixture contains substrate **1a** (0.1M), benzyltrimethylammonium hydroxide and 2,2,6,6-tetramethylpiperidinyloxyl in CH_3CN/H_2O (19:1). This reaction was performed without adding additional supporting electrolyte. Cyclic voltammetry endorses the cyclisation result, as the cyclic voltammogram in the presence of benzyltrimethylammonium hydroxide shows a lower oxidation potential from 1.69 V to 0.29 V, vs. Ag/AgCl (see Figure S2 and S3). The final oxidation potential corresponds to the deprotonated form of compound **1a**, which facilitates the generation of the radical at the anode. However, incomplete conversion of substrate **1a** to **2a** was observed with 35% yield. Then another reaction with same concentrations of reagents in CH_3CN/H_2O (19:1) was performed at 60°C with a constant current of 10 mA in a three-necked round-bottom flask equipped with a graphite anode and a platinum cathode. After 3.0 F of electricity was



Scheme 1. Substrate synthesis (**1a–t**). Reaction conditions: isocyanate (1.0 equiv), dry CH_3CN (5 mL), allylamine (1.1 equiv), 0 °C to rt, 4 h; yields of isolated products are given in Supporting Information.

passed through the electrolysis process, the substrate was consumed and the desired product **2a** was isolated in 62% yield (Scheme 2). We investigated after reactions under these conditions for the synthesis of **2b**,**c**. However, the yields were not improved significantly and decomposition of starting material



Scheme 2. Electrochemical oxysulfurisation of terminal alkenes and synthesis of thiazolidin-2-imines **2a-c**.

was observed. Then the reaction conditions were transferred toward flow electrochemistry setup (Figure 3) and first applied for the synthesis of thiazolidin-2-imines **2a**-**c** using electro-microreactor (see detail in supporting information). The reaction mixture of corresponding substrate **1** (0.025 M) with above mentioned base ($BnNMe_3OH$, 1.1 equiv) and capping reagent (TEMPO, 1.5 equiv) in CH_3CN/H_2O (19:1) was electrolysed using a graphite anode and platinum cathode with 1.0 to 3.0 F. However, the 3.0 F of electricity gave full conversion of corresponding substrate **1** to product. It was noted that the flow rates could be varied and with flow rates up to 0.2 ml/min full conversions were observed with excellent yields. Different to batch electrolysis, flow reactions were performed at room temperature (**2a-c,** Scheme 2).

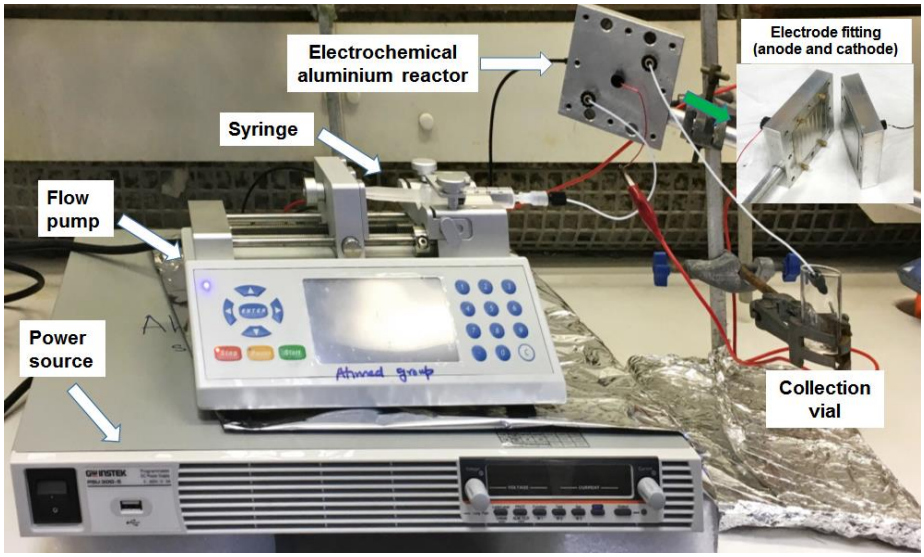


Figure 3. Electrochemical flow setup; aluminium reactor, flow pump, power source, syringe and collection vial (for flow reactions, FEP film of 500 µm thickness was used).

With the optimized reaction conditions in hand (3 F,1–3 V), more examples of thiazolidin-2-imines with the diversity of substituents on the aryl moiety (**2d-k,** Figure 4) were examined and the reaction went smoothly, while in the case of the 1-naphthyl substituted thiourea compound, the reaction was not satisfactory and only 10% conversion was observed, which could be the failure of the substrate to cyclize due to the difficulty in forming the requisite radical. The examples of thiazolidin-2-imines with a benzoyl substituent (**2l**), methylated alkene substituent (**2m)**, a benzyl substituent (**2n**), also have a good yields. However, the yields of thiazolidin-2-imines with an allyl substituent (**2o**) and a benzyl substituent (**2p**) were low (49% and 0% respectively). In these cases, the replacement of the directly attached aromatic moiety with allylic and benzyl group on the thioamide nitrogen resulted low and zero conversions of corresponding thioureas to thiazolidin-2-imines **2n** and **2p** that might be due to formation of radical intermediate with low stability. The oxygen–nitrogen bond can be cleaved with zinc and acetic acid such as we reduced one of the thiazolidin-2-imines (**2d**) to **2d-a**.[18] This functionalization gave free hydroxyl group that can be used for further functionalizations.

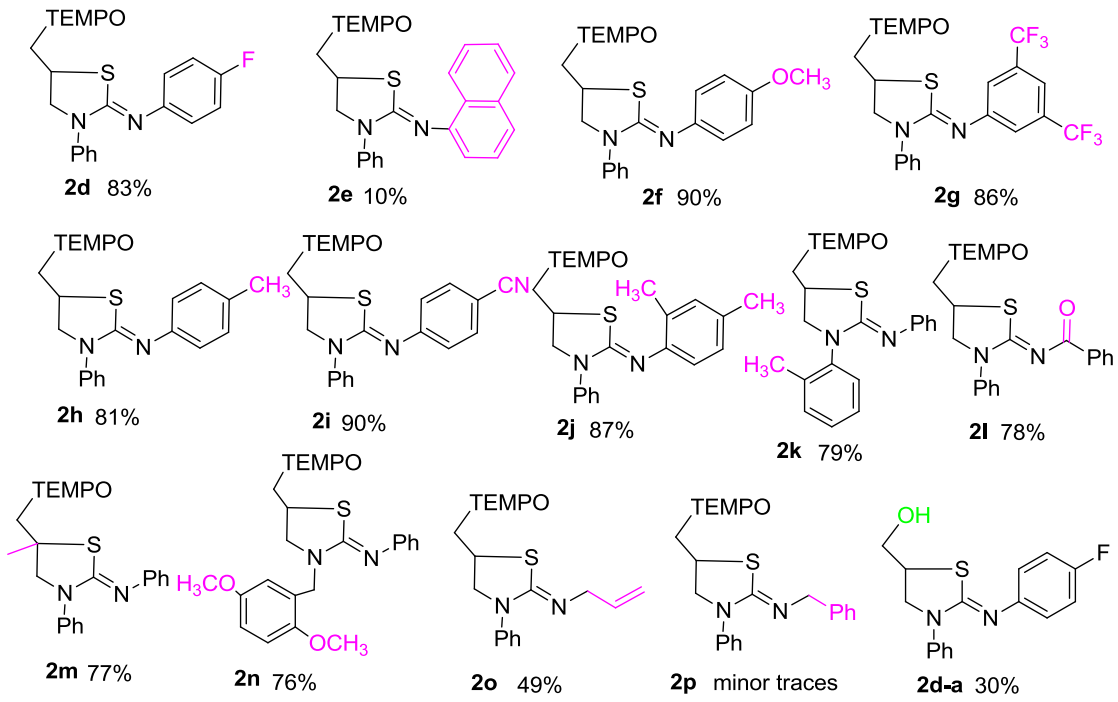


Figure 4. Substrates scope for flow electrochemical oxysulfurization of terminal alkenes end up with thiazolidin-2-imines (**2d-p**).

We have crystallised thiazolidin-2-imines **2c**, **2l** from dichloromethane and hexane (3:1) at room temperature and their X-ray analysis clearly show the cyclisation products. X-ray data of crystal **2c** (Figure 5) reveals the new bond formation of N1=C8, S1-C19, and C20-O1 with bond lengths of 1.270, 1.814, 1.427 Å respectivly. A similar result of crystal **2l** shows new bonds of N1=C8, S1-C16, and C17-O2 with bond lengths of 1.309, 1.830, 1.432 Å respectivly (see detail for **2l** in supporting information).[19] These X-ray structures show that the cyclisation gave five-membered ring thiazolidin-2-imines instead of six-membered with capping of TEMPO at the free end of terminal alkene.

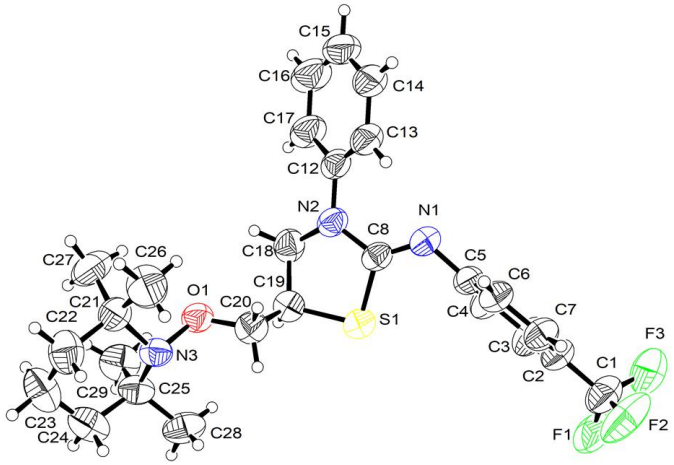


Figure 5. X-ray structure of thiazolidin-2-imine **2c**. Thermal ellipsoids are shown at 50% probability.

Under optimized reaction conditions (3 F,1–3 V), the thiourea substrates with aliphatic substituents at *N*-allylic group, led to a mixture of products showing the formation of thiazolidin-2-imines (**2q-a** to **2s-a**) and cyclic thioureas (**2q-b** to **2s-b**) with good overall yields. However, only the methyl-substituted thiourea end up with the

single product of thiazolidin-2-imine **2t**. It was observed that the presence of aryl group at both nitrogen of *N*-allylic thiourea might help in more establishing radical at sulfur and resulted in single product. However, with replacement with alkyl group causes nitrogen radical also and resulted mixture of product. The cyclic thioureas product (**2q-b** and **2r-b**) were crystallised from dichloromethane and hexane (3:1) at room temperature. X-ray data of crystal **2q-b** clearly reveals the new bond formation of N1-C3 and C15-O1, with bond lengths of 1.490, 1.431 Å respectivly, of cyclic thiourea (see detail for **2q-b** in supporting information). A similar result of crystal **2r-b** shows with new bonds of N1-C11 and C18-O1 with bond lengths of 1.487 and 1.424 Å respectivly (Figure 7).[19] These X-ray structures also show that the cyclisation gave five-membered ring cyclic thioureas with attachment of TEMPO at the free end of terminal alkene.

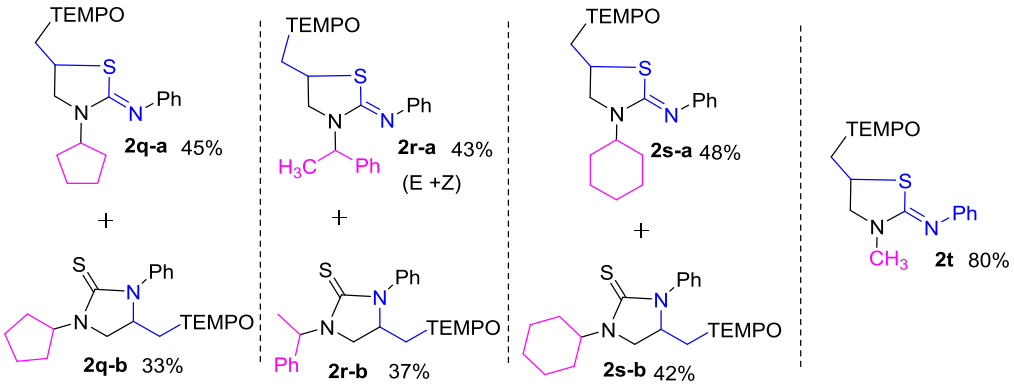


Figure 6. Substrate scope for flow electrosynthesis of thiazolidin-2-imines (**2q-a** to **2t**)

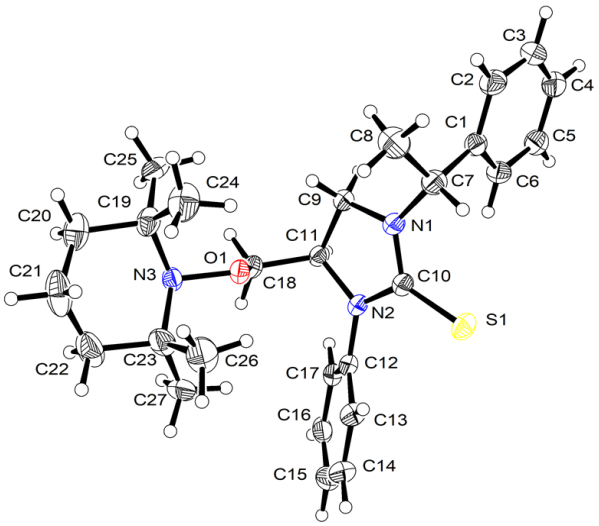
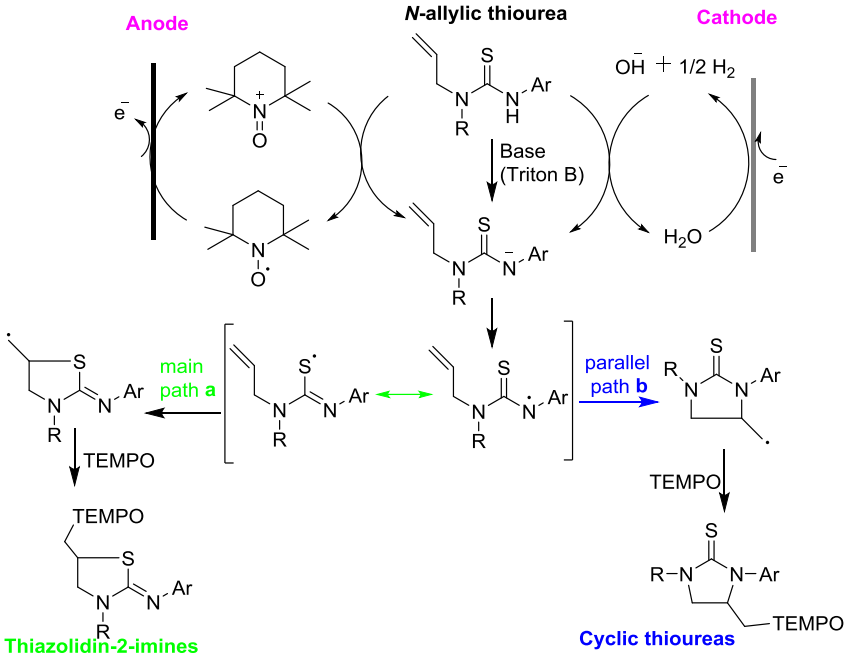


Figure 7. X-ray structure of cyclic thiourea **2r-b**.Thermal ellipsoids are shown at 50% probability.

The possible mechanism for the electrochemical cyclic products of thiazolidin-2-imines and cyclic thioureas was proposed by using N-allylic thiourea substrate (Scheme 3). The main path of radical formation at thioamide nitrogen end up with thiazolidin-2-imine product through sulfurization at terminal alkene endorsed with capping agent of TEMPO. The other parallel path that only works in few cyclisations, start with the radical formation of thioamide nitrogen and end up with cyclic thioureas. The process originates from anodic oxidation of TEMPO to oxoammonium ion and cathodic reduction of water (H_2O) to hydroxide (OH^-) and H_2. Then deprotonation of thiourea by electrogenerated hydroxide or with the base, Triton B, leads to a nitrogen-containing anion. Single-electron transfer (SET) between the anionic thiourea and the oxoammonium ion affords the nitrogen radical and regenerates

the TEMPO radical molecule. Further, in most cyclisation, nitrogen radical tautomerization with the thiocarbonyl moiety to generate a sulfur radical which undergoes the cyclization and give another radical at the terminal carbon that reacts with the TEMPO radical molecule to form the difunctionalised oxysulfurization product of thiazolidin-2-imine. In the second path of cyclization, the nitrogen radical intermediate can cyclised onto the cyclic thiourea group to give another radical at the terminal carbon that reacts with the TEMPO radical molecule to form the difunctionalised oxyamination product of cyclic urea.



Scheme 3. Possible mechanism for the synthesis of thiazolidin-2-imines and cyclic thioureas end up with alkene difunctionalization of oxysulfurization and oxyamination.

In summary, the use of flow electrochemical technology for the synthesis of fine chemicals benefits both, academia and industry. The access use of oxidants and catalysts in organic synthesis, not only increase costs for the chemists but also require a removal of reagents during the work-up procedure. The alternative using electricity as a reagent in a flow system could be the best solution of these problems and the continuous flow of getting target products in a clean way could be helpful for synthesising the chemicals at larger scale. Herein, we applied flow electro-microreactor technology to synthesise biologically important thiazolidin-2-imines in high yields, only using electricity to generate radical reaction intermediates without applying metal catalysis. We demonstrated that broad range of substrates can be cyclised under mild and environmentally friendly reaction conditions without the use of additional electrolyte. This facile methodology proceeds with excellent atom economy and endorses to avoid tedious reaction work up.

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Conflict of interest

The authors declare no conflict of interest.

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[19] CCDC 1874565 (**2c**), 1874566 (**2l**) 1874564 (**2q-b**), 1874563 (**2r-b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.